Journal of Cancer Research and Clinical Oncology
https://doi.org/10.1007/s00432-018-2822-2

ORIGINAL ARTICLE – CANCER RESEARCH

Increasing trends in in situ breast cancer incidence in a region with no population-based mammographic screening program: results from Zurich, Switzerland 2003–2014

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Received: 8 October 2018 / Accepted: 10 December 2018

Abstract

Purpose Increase in in situ breast cancer (BCIS) incidence has been reported across Europe and the USA. However, little is known about the trends in BCIS incidence in regions without population-based mammographic screening programs. We set out to investigate these trends in Zurich, Switzerland, where only opportunistic mammographic screening exists.

Methods Data from 989 women diagnosed with a primary BCIS between 2003 and 2014 were used in our analyses. Age-standardized incidence rates per 100,000 person-years (ASR) were computed per year. Additional analyses by BCIS subtype, by age group at diagnosis and by incidence period were conducted. Incidence trends over time were assessed using joinpoint regression analysis.

Results The overall BCIS ASR was 10.7 cases per 100,000 person-years with an increasing trend over the study period. A similar trend was observed for the ductal carcinoma in situ (DCIS) ASR, while the lobular carcinoma in situ (LCIS) ASR decreased. Age-specific analyses revealed that the 50–59 year age group had the highest BCIS ASR. The highest increase in BCIS ASR, even though not statistically significant, was observed for the < 40 year age group.

Conclusions BCIS ASR increased linearly over a 12-year period. The increase was reflected by an increase in DCIS ASR, whereas LCIS ASR decreased over time. The highest increase in BCIS ASR over the study period was observed for the < 40 year age group, even though not statistically significant. Patient and tumor characteristics of this group that may be associated with BCIS development warrant further investigation.

Keywords In situ breast cancer · Ductal carcinoma in situ · Lobular carcinoma in situ · Incidence · Trend · Opportunistic screening

Introduction

In situ breast cancer (BCIS) is an intraepithelial lesion with abnormal cell proliferation that can develop into invasive cancer. Two subtypes of BCIS are usually distinguished, ductal carcinoma in situ (DCIS) which accounts for the majority of BCIS cases and is diagnosed when the cell proliferation is confined in the ducts of the breast, and lobular carcinoma in situ (LCIS), where the cell proliferation remains in the lobules (Ward et al. 2015).

Over the past decades, a rapid increase in BCIS incidence has been observed both in the USA (Bleyer and Welch 2012; Virnig et al. 2010) and in Europe (Bordoni et al. 2009; Levi et al. 1997; Molinié et al. 2014; Puig-Vives et al. 2012). Most attribute this increase to the advice for mammography screening in women over 40 years of age and to the

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00432-018-2822-2) contains supplementary material, which is available to authorized users.

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Published online: 13 December 2018

implementation of population-based mammographic screening programs in many countries (Anderson et al. 2004; Baglia et al. 2018; Barchielli et al. 2005; Bleyer and Welch 2012; Gangnon et al. 2015; Levi et al. 1997).

Switzerland is a country with unique characteristics since health services are organized at the cantonal level and some health services offered to the residents are decided upon directly by the cantons (Department of Health Systems Financing HSS 2013; Herrmann et al. 2018). In some cantons, population-based mammographic screening programs are implemented (primarily in the French- and Italian-speaking regions, even though some German-speaking cantons, e.g., Bern, St. Gallen, also implement them [Eichholzer et al. 2016; Herrmann et al. 2018; International Association of Cancer Registries)], whereas in other cantons only opportunistic screening exists (Swiss Cancer Screening). Furthermore, disparities exist in the mammogram recommendation and use. Physicians in the Italian- and French-speaking regions recommend mammography screening more often compared to physicians in the German-speaking region (Federal Office of Statistics 2013; Keller et al. 2001). Additionally, women in the German-speaking region use mammography less often compared to those in the French-speaking region (34.9% vs. 77.8% of 50–69 year olds reported a mammography in the past 2 years, respectively) (Bundesamt für Statistik (BFS) 2016; Eichholzer et al. 2016).

We aimed to investigate the changes in incidence rates over time in the German-speaking Swiss canton of Zurich, where no population-based mammographic screening program was implemented and mammography use was lower than in the other Swiss regions. To the best of our knowledge, this is the first study to report BCIS incidence in the German-speaking region of Switzerland.

Materials and methods

The cancer registry of the cantons of Zurich and Zug is the largest Swiss registry covering approximately 1.6 million people. To be included in the canton's cancer registry patients have to live in the canton at the time of diagnosis, even if they are receiving treatment in another canton.

Data from women who were diagnosed with a primary BCIS (D05.0–D05.9, ICD-O-3) between 2003 and 2014 and lived in the canton of Zurich at diagnosis were used in our analyses. Registration of BCIS cases was not systematic prior to 2003, so BCIS cases diagnosed before 2003 were excluded from our analyses. Patients previously diagnosed with another type of cancer, patients with unknown or bilateral laterality, and patients for whom invasive breast cancer was diagnosed simultaneously with the BCIS were excluded from our analyses. Our final dataset included 989 women.

Breast cancers with ICD-O-3 (International Classification of Diseases for Oncology, Third Edition) morphological codes 8201/2, 8230/2, 8500/2, 8501/2, 8503/2, 8504/2 and 8507/2 were categorized as DCIS, cases with ICD-O-3 morphological code 8520/2 as LCIS, and cancers with ICD-O-3 morphological codes 8010/2, 8050/2 and 8522/2 as unspecified cancers in situ. Information on treatment, grade and socioeconomic characteristics was recorded for all patients, when available.

To calculate the proportion of BCIS compared to all breast cancers diagnosed in the canton of Zurich, we used all invasive breast cancer cases, primary or subsequent (C50.0–C50.9, ICD-O-3), diagnosed during our study period. To make our samples (BCIS vs. all breast cancers) more comparable, we imposed the same exclusion criterion of laterality, thus excluding women with unknown or bilateral laterality from the all breast cancers sample. The final all breast cancers sample included invasive breast cancer cases and BCIS cases ($n = 13{,}459$).

The Swiss neighborhood index of socioeconomic position (SEP), developed by Panczak et al., reflects the socioeconomic standing of neighborhoods based on variables including median rent, education, and occupation of household heads (Panczak et al. 2012). The SEP can range from 0 (lowest SEP) to 100 (highest SEP) and has been previously found to be associated with overall mortality, cause-specific mortality, life expectancy and other health outcomes in the Swiss population (Feller et al. 2017, 2018; Gueler et al. 2015; Moser et al. 2014; Panczak et al. 2012). Using the data recorded by the cancer registry of Zurich, we were able to determine the SEP for each patient, based on matching on the community level. In the canton of Zurich, there are approximately 130 communities, even though the number fluctuated over the study period due to merging, splitting, obliteration, and/or creation of new communities. When looking at the community level, the city of Zurich is included as one community. We used the SEP based on the communities existing on December 31st, 2010.

Statistical analyses

Baseline categorical data were expressed as counts and percentages and continuous data as medians and interquartile ranges (IQR).

Age-standardized incidence rates per 100,000 person-years (ASR) were computed using the direct method and the 1976 European Standard Population (Parkin and Muir 1992). For age-stratified analyses, we used five age groups (based on age at diagnosis, rounded down to the nearest whole number): < 40, 40–49, 50–59, 60–69 and ≥ 70 years. For analyses stratified by period of diagnosis, we used 3-year time intervals (based on the year of diagnosis): 2003–2006, 2007–2010 and 2011–2014.

Grade is not regularly documented for LCIS in pathology reports, where a different characterization may exist (classical vs. pleomorphic). However, no such information was regularly documented for our patients, thus LCIS was not included in the descriptive statistics for grade. Grade for BCIS/DCIS was defined as low (well-differentiated lesions), intermediate (moderately differentiated lesions), high (poorly differentiated lesions) or unknown, based on the patients' pathology reports.

Trends in incidence over time were assessed using joinpoint regression analysis (Joinpoint Regression Program, Version 4.6.0.0-April 2018; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). Joinpoint regression analysis is used to determine the number of joinpoints (if any) that capture the changes in incidence trends over time. The analysis starts with zero joinpoints (corresponding to a straight regression line) and tests whether the addition of one or more joinpoints is statistically significant. We defined the maximum number of joinpoints as two, the minimum number of observations from a joinpoint to either end of the data as two, and the minimum number of observations between two joinpoints as two (including any joinpoint that falls on an observation). The Grid Search Method, the Monte Carlo permutation method with 4499 replicates, log-transformation and a significance level of 0.05 were used (Kim et al. 2000; US National Cancer Institute 2018). The dependent variable was the age-standardized incidence rate; the independent variable was calendar year. In age-stratified analyses, age group at diagnosis was used as a by-variable. The average annual percentage changes (AAPC) were estimated over the whole study period (2003–2014) and were presented with 95% confidence intervals (CI).

All analyses were performed in R (Version 3.4.3) for the total population of BCIS patients ($n=989$), as well as separately by subtype of BCIS (DCIS, $n=885$, LCIS, $n=94$). Separate analyses for the unspecified cancers in situ ($n=10$) were not carried out.

Results

Patients were diagnosed with BCIS at a median age of 56.9 years (IQR: 15.9; Table 1). More than 50% of the BCIS (both DCIS and LCIS) cases were diagnosed on the left breast and the treatment of choice in two-thirds of patients was breast-conserving surgery. Patients with LCIS were diagnosed at a slightly younger age and were less likely to be married or to live with a partner compared to DCIS patients, while the SEP was similar between DCIS and LCIS patients. Approximately one-third of all DCIS cases were diagnosed with high grade. BCIS accounted for 7.3% of all breast cancer cases diagnosed in the Canton of Zurich over the study period (DCIS: 6.6% of all breast cancer cases). The highest proportion of BCIS over all breast cancer cases diagnosed was observed in 2013 (9.1% of all breast cancer cases diagnosed in 2013) (data not shown).

The overall BCIS ASR was 10.7 cases per 100,000 person-years, with BCIS increasing over the study period (from 10.1 cases per 100,000 person-years in the 2003–2006 time-period to 12.3 cases per 100,000 person-years in the 2011–2014 time-period; Table 2). Joinpoint analysis indicated a linear increase in BCIS ASR over the study period, corresponding to a statistically significant AAPC of 3.1 (95% CI 0.8, 5.5; Fig. 1).

The overall DCIS ASR was 9.5 cases per 100,000 person-years, with an increase from 8.1 cases per 100,000 person-years in 2003–2006 to 11.7 cases per 100,000 person-years in 2011–2014. On the other hand, LCIS ASR decreased over time. The overall LCIS ASR was 1.1 cases per 100,000 person-years, with a higher ASR at the beginning of the study period (1.7 cases per 100,000 person-years in 2003–2006) than in 2011–2014 (0.6 cases per 100,000 person-years). Joinpoint analysis in DCIS ASR suggested that there was a linear increase over the study period, corresponding to a statistically significant AAPC of 4.9 (95% CI 2.6, 7.4). In contrast, a decreasing linear trend was observed for LCIS, corresponding to a statistically significant AAPC of -11.6 (95% CI −20.9, −1.2; Fig. 1).

Age-specific analyses revealed that the 50–59 year age group had the highest BCIS ASR, followed by the 60–69 year age group (Fig. 2). Women younger than 40 years of age had the lowest BCIS ASR (BCIS 0.44 cases per 100,000 person-years; Online Resource 1). No joinpoints were needed for any of the age groups and only the AAPC for the 50- to 59-year-old age group was statistically significant ($AAPC_{<40}$: 5.2, 95% CI −0.1,10.9, $AAPC_{40–49}$:0.6, 95% CI −2.9, 4.2, $AAPC_{50–59}$:4.6, 95% CI 0.7, 8.7, $AAPC_{60–69}$:2.8, 95% CI −0.6, 6.3 and $AAPC_{>70}$:2.4, 95% CI −2.3, 7.4). However, the highest increase in BCIS ASR over the study period, even though not statistically significant, was observed for the <40 year age group.

Discussion

The results of this study show an increase in BCIS ASR in general and in DCIS specifically, but a decrease in LCIS ASR over a 12-year period in an area with only opportunistic mammographic screening. The trends in ASR seemed linear over the study period, both for BCIS and for the subtypes.

In our study, BCIS accounted for 7.3% of all breast cancer cases diagnosed in the canton of Zurich, whereas DCIS accounted for 6.6% of all breast cancer cases. Our results

Table 1 Clinical and socioeconomic characteristics of the total study population ($n=989$) and according to in situ breast cancer subtype

	BCIS ($n=989$)	DCIS ($n=885$)	LCIS ($n=94$)
Age at diagnosis, years	56.9 (15.9)	57.1 (16.0)	53.8 (13.7)
Time-period of diagnosis, *n* (%)			
2003–2006	293 (29.6)	239 (27.0)	47 (50.0)
2007–2010	300 (30.3)	270 (30.5)	29 (30.9)
2011–2014	396 (40.0)	376 (42.5)	18 (19.1)
Tumor characteristics			
Laterality, *n* (%)			
Right	458 (46.3)	408 (46.1)	44 (46.8)
Left	531 (53.7)	477 (53.9)	50 (53.2)
Grade, *n* (%)			
Low	239 (26.7)	237 (26.8)	NA
Intermediate	126 (14.1)	123 (13.9)	NA
High	322 (36.0)	319 (36.0)	NA
Unknown	200 (22.3)	198 (22.4)	NA
Missing	8 (0.9)	8 (0.9)	NA
Treatment, *n* (%)			
Surgery, NOS	55 (5.6)	40 (4.5)	14 (14.9)
Mastectomy	137 (13.9)	134 (15.1)	2 (2.1)
Breast-conserving surgery	645 (65.2)	578 (65.3)	60 (63.9)
Radiotherapy	79 (8.0)	76 (8.6)	2 (2.1)
Hormonal therapy	11 (1.1)	11 (1.2)	0 (0.0)
Other treatments	13 (1.3)	8 (0.9)	5 (5.3)
Missing	49 (5.0)	38 (4.5)	11 (11.7)
Patient characteristics			
Nationality, *n* (%)			
Swiss	663 (67.0)	608 (68.7)	48 (51.1)
Non-Swiss	133 (13.4)	120 (13.6)	12 (12.8)
Missing	193 (19.5)	157 (17.7)	34 (36.2)
Marital status, *n* (%)			
Never married/widowed	152 (15.4)	135 (15.3)	15 (16.0)
Married/living together	470 (47.5)	428 (48.4)	39 (41.5)
Divorced/separated	123 (12.4)	111 (12.5)	9 (9.6)
Unknown	244 (24.7)	211 (23.8)	31 (33.0)
SEP			
Total	68.9 (3.0)	68.9 (4.3)	68.9 (2.6)
City of Zurich	68.9 (0.0)	68.9 (0.0)	68.9 (0.0)
Other cities in the canton	70.6 (8.7)	70.5 (8.7)	71.2 (6.1)

Separate analyses for the unspecified cancers in situ ($n=10$) were not carried out

Expressed as median (IQR) for continuous variables and counts (percentages) for categorical variables, *BCIS* in situ breast cancer, *DCIS* ductal carcinoma in situ, *IQR* interquartile range, *LCIS* lobular carcinoma in situ, *NA* not applicable, *NOS* not otherwise specified, *SEP* Swiss neighborhood index of socioeconomic position, range: 0 (lowest) to 100 (highest)

are comparable to those reported by other European studies conducted during overlapping time-periods, where the proportion of DCIS over all breast cancer cases ranged from 6.4 to 10.4%. (Bordoni et al. 2009; Puig-Vives et al. 2012; Vanier et al. 2013) These figures are significantly lower than those reported in the USA, where DCIS accounts for almost 20% of all breast cancer cases (Kumar et al. 2005). Additionally, the increase in BCIS ASR in our study can be mostly attributed to the increase in DCIS diagnosis over time, since DCIS accounted for almost 90% of all the BCIS cases. Similarly, DCIS accounted for the majority of BCIS cases in most studies ranging from 83 to 91% of the total BCIS cases reported (Barchielli et al. 2005; Tikk et al. 2015; Ward et al. 2015).

The overall BCIS ASR in our study was 10.7 cases per 100,000 person-years, while the overall DCIS ASR was

Table 2 Incidence of in situ breast cancer (BCIS), ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), adjusted for the European standard population over the entire study period and per 4-year intervals (per 100,000 person-years)

Year of diagnosis	BCIS incidence	DCIS incidence	LCIS incidence
2003–2014	10.70	9.52	1.07
2003–2006	10.08	8.14	1.69
2007–2010	9.69	8.69	0.96
2011–2014	12.33	11.73	0.56

9.5 cases per 100,000 person-years and the LCIS ASR was 1.07 cases per 100,000 person-years over the study period. A study conducted in Girona, Spain, reported a slightly higher age-standardized population rate of 10.8 cases per 100,000 person-years for DCIS in the 2003–2007 time-period (compared to our 8.14 cases per 100,000 person-years in the period 2003–2006). However, a population-based mammographic screening program that diagnosed approximately half of the reported cases existed in Girona during the study period and could explain their higher rate (Puig-Vives et al. 2012). Furthermore, a study from Germany reported slightly lower ASR (8 cases per 100,000 person-years, in the period 1988–2007), when mainly opportunistic mammographic screening existed (Holleczek et al. 2011).

Based on data from Switzerland, the incidence of BCIS was 9.4 cases per 100,000 person-years in the time-period 1992–1994 in the French-speaking region (Levi et al. 1997), while the incidence of DCIS was 5.7 cases per 100,000 person-years in the Italian-speaking region during the time-period 1996–2007 (Bordoni et al. 2009). A different standard population was used in both aforementioned studies (the world standard population), so the findings cannot be

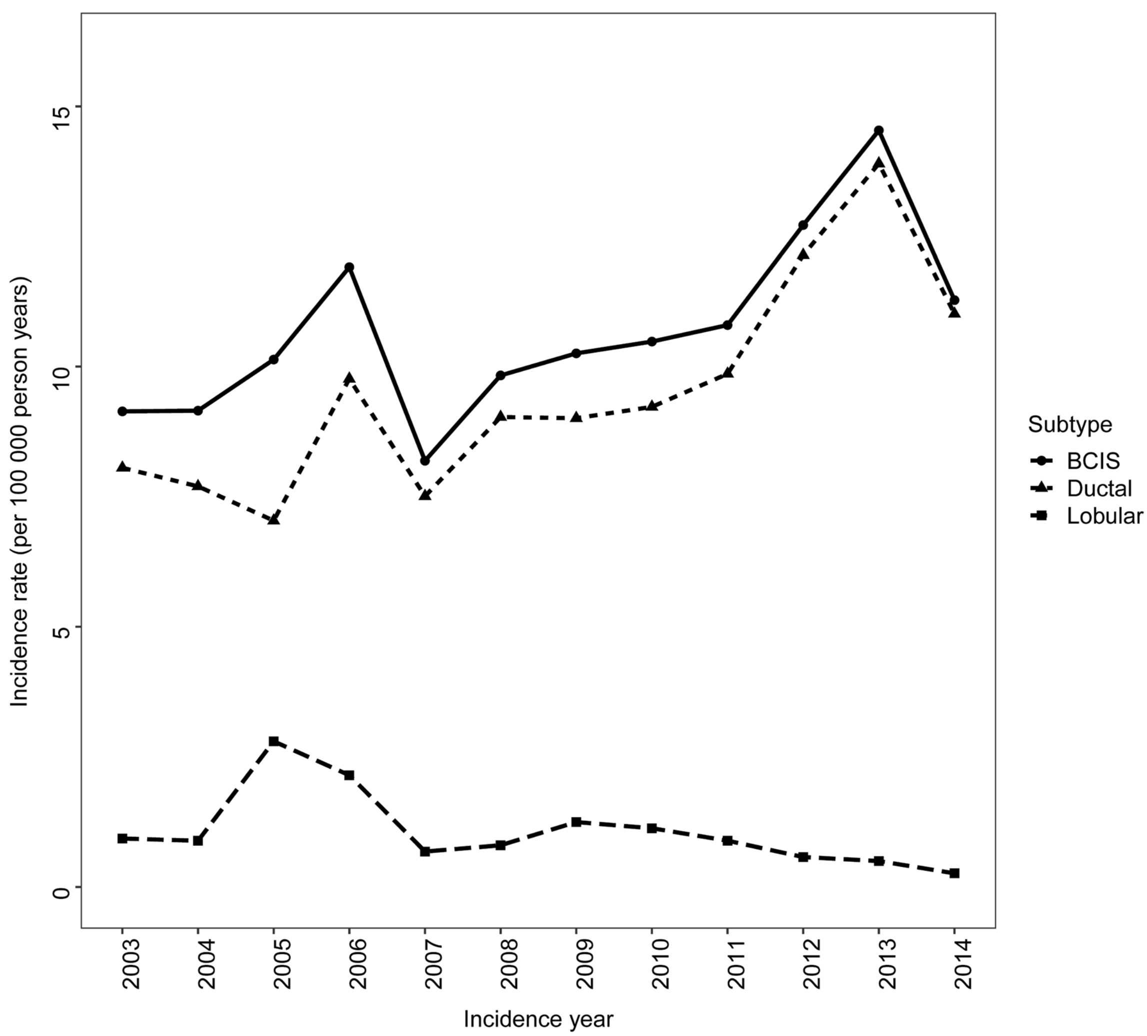

Fig. 1 Trends in incidence of in situ breast cancer (BCIS), ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), adjusted for the European standard population (per 100,000 person-years)

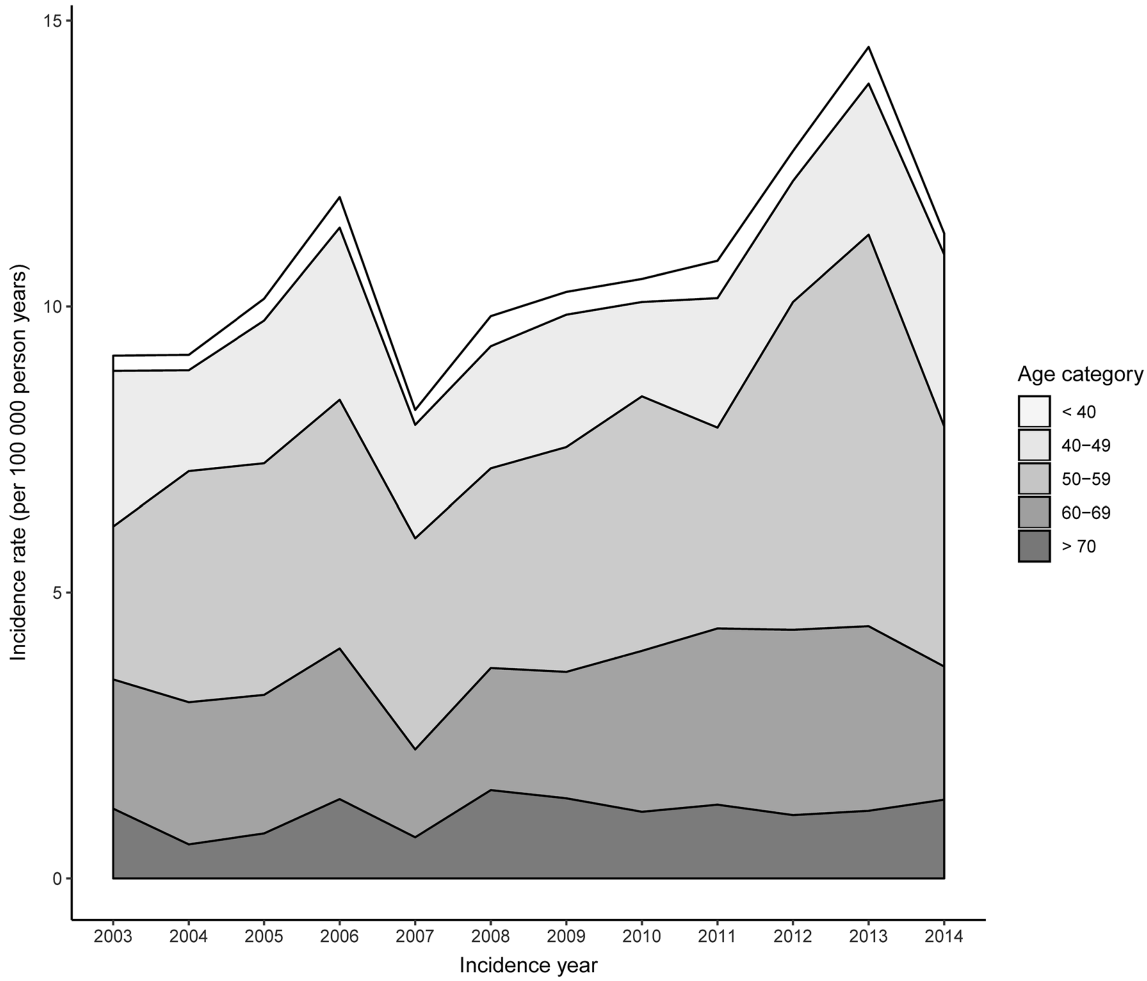

Fig. 2 Yearly incidence of in situ breast cancer (BCIS) per age category at diagnosis, adjusted for the European standard population (per 100,000 person-years)

directly compared to ours. Additionally, both studies preceded ours, so they cannot be used for comparison but can give us only an indication of BCIS incidence in these regions during the study periods.

Approximately one-third of the BCIS diagnosed in our study had high grade, corresponding to poorly differentiated BCIS lesions. Our proportions of high-grade BCIS are slightly higher than those reported in the Italian-speaking Swiss region (Bordoni et al. 2009), but significantly lower than those reported in a Norwegian study (Sørum et al. 2010). An increase in mammography in women 50–69 years old has been reported in Switzerland, with 80% of the women in this age group having had a mammogram at least once in their life (Federal Office of Statistics 2013). This increase coincides with the initiation of population-based mammographic screening programs in this specific age group (e.g., the Swiss Cantons of Geneva and Vaud both initiated screening programs in 1999) (Herrmann et al. 2018; International Association of Cancer Registries). Upon the introduction of mammographic screening programs, studies have shown that the number of early-stage breast cancer doubled (Bleyer and Welch 2012). Additionally, a lower proportion of women undergoes mammography in the German-speaking regions compared to the French-speaking regions (34.9% vs. 77.8% of 50–69 year olds reported a mammography in the past 2 years, respectively) (Bundesamt für Statistik (BFS) 2016; Eichholzer et al. 2016). Thus, it is possible that BCIS lesions in our study population progressed to higher grade before detection compared to lesions detected in other cantons where population-based mammographic screening programs are implemented and mammography use is higher. The aforementioned hypothesis is supported by the literature that suggests that BCIS gradually evolves from low grade (well-differentiated lesions) to high grade by acquiring genetic mutations (Allred et al. 2008).

The highest increase in BCIS ASR over the study period was observed for the <40 year age group (AAPC <40: 5.2, 95% CI -0.1, 2.2), even though it was not statistically significant. This finding is in agreement with the increase in breast cancer incidence in this age group reported in the literature (Arleo et al. 2015; Bouchardy et al. 2007; Merlo et al. 2012; Pollán et al. 2010). Based on the Swiss Health Survey, 44% of women 40–49 years old had already had a mammography screening at least once. This indicates that younger women in Switzerland use mammography and further supports our finding (Federal Office of Statistics 2013). Using mammography was statistically significantly associated with higher incidence of in situ and/or localized breast cancer (Gangnon et al. 2015; Yoshida et al. 2018). Since BCIS is primarily detected by mammography screening, the increasing use of mammography in that age group and detection bias could explain the increase in ASR we detected in our population. However, as previous studies have pointed out, the effect of possible risk factors should be considered and investigated further (Arleo et al. 2015; Bouchardy et al. 2007).

We hypothesize that the use of mammography increased over time, resulting in an increase in the incidence of BCIS and early-stage invasive breast cancer. As the number of mammography-detected breast cancer cases increased in the USA, the number of BCIS cases increased as well, indicating that mammographic screening may have led to a shift to lower stage breast cancer (Malmgren et al. 2008). Similarly, women aged 50 and older living in Swiss cantons with organized mammographic screening programs showed a shift to earlier breast cancer stage (in situ and localized) compared to women in cantons with only opportunistic screening (Feller et al. 2017). Additionally, the proportion of women with stage I breast cancer increased from 38.1% in 1996–2001 to 42.2% in 2002–2007 in a region where only opportunistic screening existed (Bordoni et al. 2009). The aforementioned studies support the hypothesis that increase in mammography is reflected in the increase in BCIS and early-stage invasive breast cancer. However, no significant increase in the proportion of women aged 50–69 years old who have undergone a mammography screening in the past 2 years in the German-speaking region was reported in the Swiss Health Surveys between 2002 and 2012 (Bundesamt für Statistik (BFS) 2016). This suggests that risk factors, other than mammography use, should be further investigated for the increase in BCIS and early-stage invasive breast cancer.

Our study had several strengths. Registry coverage in the Canton of Zurich is high, such that we are confident we capture almost all incident BCIS cases in the canton (Wanner et al. 2018). Additionally, medical and treatment information, as well as patient and tumor characteristics were documented for a high proportion of our study population.

However, this study also has some limitations. Information on variables such as family history, genetic polymorphisms, parity, and age at first birth that have been associated with BCIS risk was not available. Furthermore, information on lymph node status was missing in most cases; thus, we were not able to include it in our analyses. Due to the small number of BCIS cases per year, incidence fluctuations were observed between years. Finally, since distinction of cases as LCIS or lobular neoplasia may not be clear [the term lobular neoplasia includes both LCIS and atypical lobular hyperplasia (Lakhani 2012)] and sometimes they seem to be used interchangeably in clinical practice, we cannot exclude the possibility of misclassification. Thus, the decrease in LCIS incidence could potentially be due to changes or differences in case registration between the earlier and later years in our study.

In conclusion, BCIS ASR increased linearly over a 12-year period in the canton of Zurich. The increase was reflected by an increase in DCIS ASR, whereas LCIS ASR decreased over time. The highest BCIS ASR was observed in the 50–59 years age group, but the highest increase in BCIS ASR was documented in the < 40 years age group. Additional studies are needed to document BCIS incidence in regions without population-based mammographic screening programs and to investigate patient and tumor characteristics that may be associated with BCIS development.

Funding NK is funded by Cancer Research Switzerland (grant number KFS-4114-02-2017) and ML is funded by Cancer League Zurich.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Cancer cases in the Canton of Zurich are registered with presumed consent and registration based on a decision by the Zurich Government Council from 1980 and the general registry approval by the Federal Commission of Experts for professional secrecy in medical research from 1995. All data were used anonymously in this analysis, and no approval from the Ethical Committee of the Canton of Zurich was necessary.

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